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Remarks

Upon entry of the foregoing amendments, claims 1-21 are pending in the application. The amendment to the claims do not present any new matter. Support for the changes to the claims may be found throughout the application generally and, specifically, in the claims as originally filed. Applicants attach hereto a version of the claims showing changes made by the current amendment. Applicants wish to thank Examiner Lee for his time in discussing the Office Action of March 3, 2004, with Eric Middlemas by telephone on April 2, 2004.

Restriction Requirement

In response to the Examiner's restriction requirement, applicants hereby affirm the provisional election of Group I with traverse. Applicants submit that the restriction requirement is improper because the process of Group II is not independent and distinct from the catalyst system of Group I as required by 35 U.S.C. §121. There is a clear, disclosed relationship between the catalyst system of Group I and the process of Group II which includes the catayst systems of Group I. The novelty of the process of Group II resides in the catayst system of Group I. Moveover, the primary application of the catalyst of Group I is to produce an aldehyde by the process of Group II. In addition, Applicants respectfully submit that search and examination of the entire application on the merits will not present an undue burden on the Examiner. Reconsideration and withdrawal of the restriction requirement is respectfully requested.

Claim Objections

In response to the Examiner's objections to the claims, applicants have amended Claims 1-4 and 7, 8, and 10 substantially in the manner suggested by the Examiner in paragraphs 7-12 of the the Office Action. As is shown on the pages of revised claims provided herewith, the second instance of the term "comprising" has been deleted from Claim 1. The term "about" has been removed when used in reference to the number of carbon atoms in claims 2-4, 7, 8, and 10. The term "of" has been inserted after the word

"content" in claim 2. Applicants, however, respectfully maintain that the the word "separate" instead of "separately" is the proper term to modify the term "hydrocarbyl radicals", meaning that the hydrocarbyl radicals may exist as independent entities instead of being combined or joined together.

Claims 3, 8, and 10 have been rewritten to delete the term "individually" when used together with the term "independently" as suggested by the Examiner. In addition, the term "such" has been replaced with the term "said", again in accordance with the Examiner's suggestion.

Rejection of Claims 1 and 3-11 under 35 U.S.C. §112

The Examiner has rejected claims 1 and 3-11 under 35 U.S.C. §112 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Although applicants respectfully traverse the rejection and the statements in support thereof, claims 1 and 3-11 have been rewritten to incorporate the Examiner's suggestions and to advance the prosecution of the instant application.

Claims 1 and 7 have been amended to clarify that the Group VIII metal or Group VIII metal-containing compound does not include rhodium. Applicants believe that the language of the amended claims clearly points out and defines the invention.

Claims 3 and 8-11 have been rewritten to correct the allegedly improper Markush language. Claims 3, 4, 6, and 7 have been rewritten to substitute the term "fluorophosphite ligand" for "fluorophosphite compounds". This change provides a proper antecedent basis for language of these claims and for dependent claims 5 and 8-11. Similarly, the term "dihydrocarbyl" has been deleted from claim 6. Applicants believe that rewritten claim 6 has proper antecendent support.

Claims 9 and 11 have been rewritten to delete the phrase "which are liquid at the pressure at which the process is being operated". Because the term "the process" is no longer recited in the rewritten claims, the rejection is no longer believed to be at issue.

Rejections under 35 U.S.C. § 103

Claims 1-11 are rejected under 35 U.S.C. § 103 (a) over U.S. Patent No. 5,840,647 to Puckette *et al* ("Puckette") in view of U.S. Patent No. 5,756,855 to Abatjoglou *et al* ("Abatjoglou"). Applicants respectfully traverse the rejection and the statements made in support thereof.

A proper analysis under §103 requires, *inter alia*, consideration of whether the prior art would have taught or suggested to one of ordinary skill in the art both that they should carry out the claimed invention and that there is a reasonable expectation of success in doing so. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the motivation to combine the cited references must be found in the prior art. *Id.* The prior art must teach or suggest all of the claim limitations. See In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As set forth below, neither the required teaching of the invention, the motivation to combine references, nor the expectation of success is found in the cited art.

The primary reference cited by the Examiner, Puckette, discloses a catalyst system comprising one or more transition metals selected from the Group VIII metals and rhenium and one or more fluorophosphite compounds. Puckette describes in general the reactive properties of halophosphorus compounds, including their known tendency to hydrolyze in the presence of water and other hydrolytic solvents to produce hydrogen halides (see col. 2, lines 43-67, through col. 3, lines 1-17). Puckette, however, makes no suggestion or teaching that fluorophosphites undergo hydrolysis similar to other halophosphites or that fluorophosphites produce any amount of HF while being used as part of a catalyst system. In fact, Puckette underscores the stability of fluorophosphites in comparison to the known chemistry of other halophosphites and notes that their properties are "contrary to the teachings of the prior art" (see col. 3, lines 19-27). There is simply no mention of HF, the decomposition of fluorophosphites, or of any stability concerns associated with fluorophosphite compounds anywhere within Puckette. Further, as noted by the Examiner, Puckette does not recite the use of a

Group VIII metal in conjunction with rhodium to reduce the formation of HF. Thus, a person of ordinary skill in the art, based on the disclosure of Puckette, would have had no motivation to seek a method to reduce the formation of HF during the use of a fluorophosphite catalyst system and, certainly, no motivation to use a Group VIII metal, other than rhodium, to do so.

The disclosure of Abatjoglou fails to cure the deficiencies of Puckette. Abatjoglou discloses a hydroformylation process using a triorganophosphite, rhodium, and a Group VIII metal other than rhodium in an amount sufficient to reduce the rhodium-catalyzed decomposition of the phosphite ligand. The process disclosed by Abatjoglou is directed explicitly toward the rhodium-catalyzed decomposition of triorganophosphites with specific structural features that exclude fluorophosphites:

> The phosphite ligands useful in the process of the present invention contain one or more trivalent phosphorus atoms and each valence of the phosphorus atom bonds the phosphorus atom to a carbon atom of an aromatic ring through an oxygen atom and that carbon atom of at least one of the aromatic rings is adjacent to another carbon atom of the aromatic ring to which is bonded a pendant monovalent group (hereinafter called "hindering group") having a steric hindrance at least as great as the steric hindrance of the isopropyl group. (Abatjoglou, col. 3, lines 13-22).

In addition, the disclosure of Abatjoglou provides no suggestion or motivation to apply any element of the triorganophosphite catalyst system to the fluorophosphite system of Puckette. In fact, Abatjoglou is absolutely silent regarding fluorophosphites, their stability, or the formation of HF. Moreover, the phosphite decomposition process disclosed by Abatjoglou involves the formation of rhodium clusters, a process entirely different from the formation of HF (see col. 20, lines 11-29). That such clusters may be associated with phosphite decomposition, in fact, teaches away from Puckette, which discloses that rhodium clusters are useful catalysts in combination with fluorophosphites (see Puckette, col. 6, line 67 through col. 7, lines 1-2).

These differences are substantial and difficult to dismiss. Within any reasonable context, neither Puckette nor Abatjoglou would have taught applicants' invention or would have provided any motivation to the skilled person to combine their disclosures. The skilled artisan, on reading Puckette, simply would not have looked to Abatjoglou to

solve a problem which is never mentioned or suggested to exist. Similarly, Abatjoglou provides no motivation to seek out the disclosure Puckette and, in fact, would have steered the skilled person completely away from the fluorophosphites of Puckette.

The Office Action states that "such a procedure is routine in the art." Although it is unclear to which procedure the Office Action refers, applicants respectfully disagree with the assertion that the processes disclosed by Puckette or Abatjoglou would be considered "routine" to a person of ordinary skill in the art. Applicants further submit that, in the absence of hindsight, there is no established procedure, understanding, or principle within the knowledge of a skilled artisan that would have motivated a skilled person to select elements from the cited documents and to make the present invention with any reasonable expectation of success. For example, the reactivity and, hence, the stability of phosphites are known to vary widely and depend strongly on their structure (see, for example, Van Leeuwen et al. *Rhodium Catalyzed Hydroformylation*; Kluwer Academic Publishers, 2000, pp 243-247, enclosed herewith). This fact is illustrated further by the distinct differences in reactants and processes disclosed by Abatjoglou and the instant application. The phosphite decomposition process disclosed by Abatjoglou occurs over a period of 12 days (Abatjoglou, col. 3, lines 31-37). By contrast, the formation of HF described in the present application takes place over a period of 5 hours (see Comparative Example 1 of the present application). In view of the differences in these processes and known variability in the reactivity of phosphites, the cited art, even if considered by a person of ordinary skill in the art, could not have provided a reasonable expectation of success for the present invention.

Applicants respectfully submit that the stated rejection fails to establish a *prima facie* case of obviousness. First, the cited references do not suggest or teach applicants' invention. In fact, as noted above, there are distinct elements within the cited references that teach away from the present invention. Second, the Office Action does not show from the cited art a proper suggestion or motivation to combine references. The "showing of a suggestion, teaching, or motivation to combine prior teachings "must be clear and particular...Broad conclusory statements regarding the teaching of multiple

references standing alone, are not 'evidence'". See *In re Dembiczak*, 175 F.ed 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Further, there must be a "rational connection between the facts found and the choice made." See *In re Lee* 61 U.S.P.Q. 2d 1430 (Fed. Cir. 2002). Here there is no such rational connection between that which is taught in the cited references and the elements of the presently claimed invention. Applicants respectfully submit that the motivation stated by the Office Action is broad, does not point to applicants' fluorophosphites catalyst system and, in the absence of hindsight, would not have motivated a person skilled in the art at the time the invention was made to look to the cited sources of information, to select particular elements, and to combine them to obtain Applicants' claimed process.

Finally, because of the lack of a suggestion or teaching of Applicants' process, the cited art necessarily could not have provided a reasonable expectation of success. It is applicants' respectful view that the stated rejection requires selection of only certain features of the cited art and discards or ignores other features that teach away from the claimed invention using applicants' disclosure as a template. Applicants, therefore, respectfully request reconsideration and withdrawal of the rejection.

In summary, Applicants believe that Claims 1-11 as amended are patentable over the cited art, whether considered alone or in any reasonable combination. Accordingly, the withdrawal of all the rejections and early allowance of the application are earnestly requested.

Respectfully submitted,

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April 8, 2004
Date

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

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RHODIUM CATALYZED HYDROFORMYLATION

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Chapter 9

Catalyst preparation and decomposition

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9.1 Introduction

Catalyst preparation or setting up the catalytic system is closely related to the decomposition of the catalysts. In this chapter we will deal with both aspects. Rhodium hydroformylation catalysts can decompose in a variety of ways: metal deposition, ligand decomposition, reactions with impurities, dimer formation, and reaction of the metal center with the ligand. Sometimes these side-reactions lead to temporary deactivation only and the catalyst activity can be restored. Without attempting to be complete, we have collected several examples of catalyst decomposition. In the area of homogeneous catalysis there has always been less attention, certainly in chemistry journals, for the stability, decomposition, and regeneration of the catalyst as there is in the area of heterogeneous catalysis. This does not mean that stability of the catalyst is not an issue, on the contrary. For the many industrial applications that have come on stream in the last three decades, catalyst stability has been a key issue, next to selectivity and activity. In industry a considerable effort has been devoted to the study of catalyst stability even though few accounts were published in patents or journals. Many examples that we will mention stem from the work of the Bryant group at Union Carbide Corporation.

9.2 Catalyst preparation

The "catalyst" for hydroformylation is a rhodium(I) hydride species that is clearly distinct from the species that are active for hydrogenation. The

P.W.N.M. van Leeuwen and C. Claver (eds.), Rhodium Catalyzed Hydroformylation, 233–251.

hydrogenation catalysts are cationic $Rh(I)^+$ or neutral Rh(I)Cl species. Carbonylation of alcohols also requires an anionic Rh(I) species, e.g. $[Rh(CO)_2I_2]^-$. In modern catalysis we want to know the exact nature of our catalysts and we would like to control its formation and stability.

Often rhodium(I) salts are used as the precursor for hydroformylation catalysts. Under the reaction conditions (H_2, CO, ligands, temperature > 25 °C) these salts are converted to a rhodium hydride complex, although there are several papers that seem to invoke cationic rhodium species as the catalysts. A catalyst that does contain another rhodium species is the one reported by Stanley, containing bimetallic rhodium species [Chapter 10]. Anions that have been used include halides, conjugate bases of weak acids, thiolates, alkoxides, etc. Chlorides have a particular deleterious effect on the activity (i.e. they are not converted into hydrides under mild conditions). Chloride may be present in phosphites or phosphines as a result of the synthesis; especially when the ligands are used in a large excess this may be the cause for low activities. It has been reported that addition of bases such as amines has a strong "promoting" effect on such systems:

$$L_3RhCl + H_2 + CO + R_3N \rightleftharpoons L_3Rh(CO)H + R_3NH^+Cl^-$$

Rhodium salts of weaker acids are smoothly converted into rhodium hydride without the addition of base:

$$L_3RhA + H_2 + CO \rightleftharpoons L_3Rh(CO)H + HA$$

A = acetate, 2,4-pentanedionate

When a large excess of carboxylic acid is present, rhodium carboxylate is not converted into hydride [1]. A preferred dionate is 2,2,6,6-tetramethyl-3,5-heptanedionate (dipivaloylmethane) especially because its solutions are stable upon storage [2]. The use of stock solutions is recommended because very small amounts of rhodium need to be applied when active catalysts are being studied. In batch reactions the formation of rhodium hydride species may be slow compared to catalysis. If so, one should pre-heat the catalyst system to allow the formation of the catalyst before adding the alkene.

As will be discussed in section 9.3 purification of the reagents is important as impurities may lead to decomposition of the catalytic precursor.

metal in the system. Therefore, oxygen and hydroperoxides have to be thoroughly removed from the reagents and solvents before starting our catalysis. In spite of this common knowledge oxidation of phosphine ligands has frequently obscured the catalytic results. Purification of the alkene feed is often neglected. Since the alkene may be present in a thousand-fold excess of the ligand, careful removal of hydroperoxides in the alkene is an absolute must. Hydroperoxides are the ideal reagents for oxidizing phosphines. Percolation over neutral alumina is usually sufficient for a hydroformylation reaction. Treatment over sodium or sodium-potassium on a support will also remove alkynes and dienes that may influence the catalyst performance. Distillation from sodium may give isomerization of alkenes as an undesirable side-reaction.

Practical recommendations and safety aspects. During the set-up of the experiments air has to be excluded, although the reaction of oxygen with electron-poor phosphorus compounds is much slower than that with components of Ziegler like catalysts for instance. A simple calculation may be useful. Suppose one uses an autoclave having a volume of 100 mL containing 10 mL of solvent and a catalyst concentration of 1 mM, and a tenfold excess of phosphine ligand (10 mM). The autoclave contains 0.1 mmole of phosphine. Thus, assuming a stoichiometry of one dioxygen for two phosphine molecules we need as little as 6 mL of air to oxidize the phosphine inventory! Flushing the tubing, pressurization and depressurization of the autoclave with syn-gas, or evacuation, and cannula and syringe techniques suffice to exclude oxygen in the system.

One can circumvent the problems caused by ligand oxidation by adding an excess of the ligand, unless one is interested in the kinetics in relation to the type of complexes present in the system. This and the addition of triethylamine lead to a fast and practical way of doing hydroformylation reactions. With these precautions the reaction is a highly accessible one for people less experienced in catalysis. High-pressure equipment remains a prerequisite (10 bar); we recommend the use of autoclaves, regularly tested by the workshops, even though glassware for carrying out reactions at 5 bar might be available.

The safety issues for working with high pressures, phosphorus compounds, and syn-gas are well recognized. For high pressures and syn-gas there will usually be government regulations concerning the construction, maintenance, testing, and use of the equipment. For syn-gas one finds a detection system in many laboratories and a regular rehearsal on how to act when the alarm rings. Depressurization of the autoclaves (< 250 mL, < 20 bar) is done in the fume cupboards using a tube ending in the exhaust channel. The rate of depressurization should be such that in the exhaust gas the MAC value of CO is not exceeded.

The most commonly used phosphines such as tpp, tppms, and tppts have been well tested for their toxicity owing to their use on industrial scale. No particular dangers have been reported. The same holds for many phosphites, which are also marketed as anti-oxidants. Apart from these compounds the phosphorus compounds and their intermediates should be handled with the same care as the toxic analogs that are known. Toxicity levels may be comparable to common agrochemicals. Below we show one example of such a group of phosphite ligands that turned out to be toxic (Table 1, Figure 2). Most of the ligands we are using in the laboratory have not been tested.

Table 1. Toxicity data for a few phosphites [6]

Structure	LD_{50} (mg/kg, for mice, Intraperitoneal)
R= CH_2OH (Figure 2)	> 500
R= Et (Figure 2)	1.1
R= Pr (Figure 2)	0.39
R= i-Pr (Figure 2)	0.22
Parathion (as P=S)	5.9
DFP (as P=O)	6.0

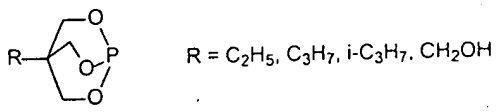

Figure 2. Structure of some toxic phosphites

9.3.3 Phosphorus-carbon bond breaking in phosphines

Oxidation of free phosphines was mentioned above as a reaction leading to phosphine loss. Here we will discuss three further ways of phosphine decomposition: oxidative addition of phosphines to low-valent metal complexes, nucleophilic attack on coordinated phosphines, and aryl exchange via phosphonium species. Interestingly in all cases the metal serves as the catalyst for the decomposition reaction!

In his review [7] and feature article [8] (entitled "I wonder where the ligand went"!) Garrou emphasizes the first mechanism, oxidative addition of the phosphorus-carbon bond to low-valent metal complexes. More recently experimental support for the other two mechanisms has been reported. In Figure 3 the three mechanisms are briefly outlined.

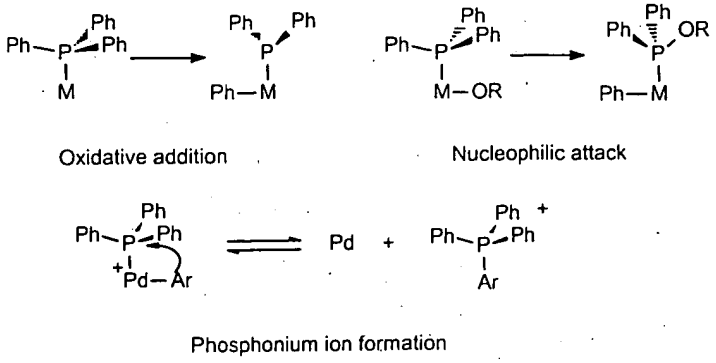

Figure 3. Phosphorus-carbon bond breaking

The latter mechanism has only been observed for palladium compounds as yet, although it would also be feasible for rhodium(I) compounds giving an anionic rhodium species and a phosphonium fragment. The actual phosphorus carbon bond breaking occurs upon the reverse reaction, when the phosphonium ion adds oxidatively to a low-valent metal.

Oxidative addition of P-C bond to a low-valent metal. Oxidative addition of C-Br or C-Cl bonds is an important reaction in cross-coupling type catalysis, and while the reaction of a P-C bond is very similar, the breaking of carbon-to-phosphorus bonds is not a useful reaction in homogeneous catalysis. The reverse reaction, making of a carbon-to-phosphorus bond via palladium or nickel catalysis, is becoming increasingly more important for the synthesis of new phosphines [9]. P-C bond breaking is an undesirable side-reaction that occurs in systems containing transition metals and phosphine ligands and it leads to deactivation of the catalysts. The oxidative addition of a phosphine to a low-valent transition-metal can be most easily understood by comparing the Ph_2P- fragment with a Cl- or Br- substituent at the phenyl ring; electronically they are very akin, c.f. Hammett parameters and the like. The phosphido anion formed during this reaction will usually lead to bridged structures, which are extremely stable. Decomposition of ligands during hydroformylation has been reported both for rhodium and cobalt catalysts [10-12].

Thermal decomposition of $RhH(CO)(PPh_3)_3$, in the absence of H_2 and CO, leads to a stable cluster shown in Figure 4 containing μ_2-PPh_2 fragments [13] as was studied by Bryant's group at Union Carbide. Presumably clusters of this type also form in hydroformylation plants on the long run. Recovery of rhodium from these inert clusters is a tedious operation. Reaction of the cluster mixture with reactive organic halides such as allyl chloride has been described to give allyldiphenylphosphine and rhodium chloride, which can be easily extracted into a water layer. [14].

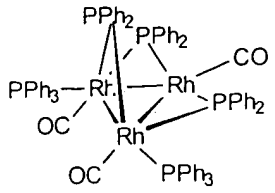

Figure 4. Rhodium cluster formed from decomposition of $RhH(PPh_3)_3CO$

Under hydroformylation conditions also other products are found such as benzaldehyde, benzene, and diphenylpropylphosphine. The mechanism for their formation is outlined in Figure 5.

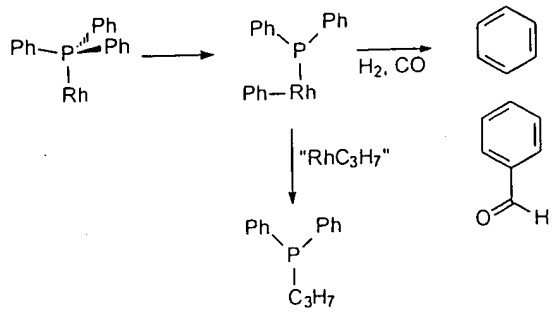

Figure 5. Formation of side-products during ligand decomposition

The phenyl group formed ends up as its hydrogenation or carbonylation product. Instead of cluster formation the phosphido group may give a reductive elimination starting from a rhodium propyl species, which gives diphenylpropylphosphine as the product. The disadvantage of this phosphine is that it is a stronger electron-donor than tpp and it leads to a less active rhodium catalyst. Thus at some stage it has to be removed, which can be done by utilizing its higher basicity by selective phosphonium salt formation.

Benzene and benzaldehyde byproducts were also observed in the Ruhrchemie-Rhône Poulenc process using the trisulfonated analog of triphenylphosphine [15], but the decomposition was reported to be much slower for tppts as compared to tpp. This is an accidental favorable aspect of the RC-RP process; it is unexpected because water might oxidize the phosphine, or it might carry out a nucleophilic attack, thus initiating the second mode of decomposition (vide infra).

Cluster or bimetallic reactions have also been proposed in addition to monometallic oxidative addition reactions. The reactions do not basically change. Several authors have proposed a mechanism involving orthometallation as a first step in the degradation of phosphine ligands,

especially in the older literature. orthometallation does take place as can be inferred from deuteration studies, but it remains uncertain whether this is a reaction necessarily preceding the oxidative addition (Figure 6):

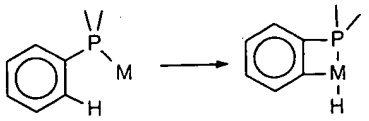

Figure 6. Orthometallation

Subsequently the phosphorus-to-carbon bond is broken and the benzyne intermediate inserts into the metal hydride bond. Although this mechanism has been popular with many chemists there are many experiments that contradict this mechanism. A simple para-substitution of the phenyl group would answer the question whether orthometallation was involved as is shown in Figure 7:

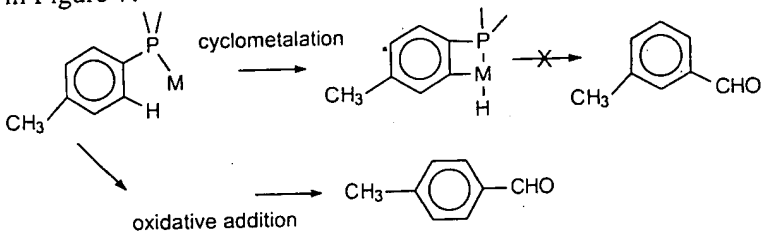

Figure 7. Disproof of orthometallation as the mechanism for P-C cleavage

Decomposition products of tolylphosphines should give 3-methyl substituents if the orthometallation mechanism is operative. For palladium catalyzed decomposition of triarylphosphines this is not the case [16]. Likewise, Rh, Co, and Ru hydroformylation catalysts give aryl derivatives not involving C-H activation [17, 18]. Several rhodium complexes catalyze the exchange of aryl substituents at triarylphosphines [18]:

$$R'_3P + R_3P \text{ —(Rh)—> } R'R_2P + R'_2RP$$

These authors propose as the mechanism for this reaction a reversible oxidative addition of the aryl-phosphido fragments to a low valent rhodium species. A facile aryl exchange has been described for complexes $Pd(PPh_3)_2(C_6H_4CH_3)I$. Again the authors [19] suggest a pathway involving oxidative additions and reductive eliminations. The mechanism outlined below, however, can also explain the results of these two studies.

Phosphido formation has been observed for many transition metal phosphine complexes [7, 8]. Upon prolonged heating and under an

atmosphere of CO and/or H_2 palladium and platinum also tend to give stable phosphido bridged dimers or clusters [20, 21].

Nucleophilic attack. Current literature underestimates the importance of nucleophilic attack as a mechanism for the catalytic decomposition of phosphines, especially with nucleophiles such as acetate, methoxy, hydroxy and hydride. For examples of nucleophilic attack at coordinated phosphorus see references [20-25]. A very facile decomposition of alkylphosphines and triphenylphosphine (using palladium acetate, one bar of hydrogen and room temperature) has been reported [20] using acetate or hydride as the nucleophile.

A detailed reaction proving the nucleophilic attack was shown for platinum complexes [25]. The alkoxide coordinated to platinum attacks phosphorus while the carbon atom coordinated to platinum migrates to phosphorus. Thermodynamically the result seems more favorable, but mechanistically this "shuffle" remains mysterious (see Figure 8). Coordination to platinum makes the phosphorus atom more susceptible to nucleophilic attack, and the harder atoms (P and O) and softer ones (C and Pt) recombine as one might expect. The same mechanism was proposed by Matsuda [22] for the decomposition of triphenylphoshine by palladium(II) acetate. In this study the aryl phosphines are used as a source for aryl groups that are converted into stilbenes via a Heck reaction. Even alkyl phosphines underwent P-C bond cleavage via palladium acetate.

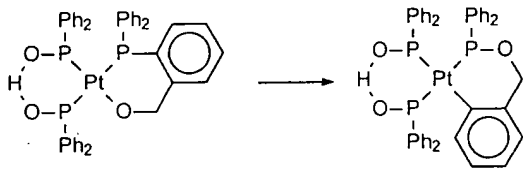

Figure 8. Intramolecular nucleophilic attack

A catalytic decomposition of triphenylphosphine has been reported [26] in a reaction involving rhodium carbonyls, formaldehyde, water, and carbon monoxide. Several hundreds of moles of phosphine can be decomposed this way per mole of rhodium per hour! The reactions that may be involved are shown in Figure 9.

Related to this chemistry is the hydroformylation of formaldehyde to give glycolaldehyde, which would be an attractive route from syn-gas to ethylene glycol. The reaction can indeed be accomplished and is catalyzed by rhodium arylphosphine complexes [27], but clearly phosphine decomposition is one of the major problems to be solved before formaldehyde hydroformylation can be applied commercially.

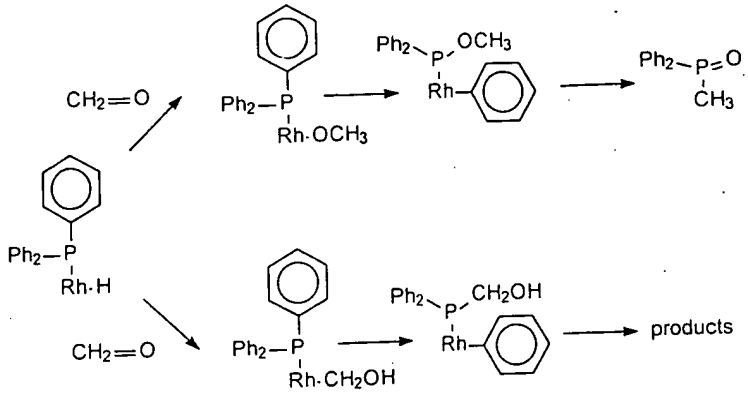

Figure 9. Catalytic decomposition of tpp by formaldehyde and hydrogen

The interest in cross-coupling reactions in the last decade has lead to a large number of reports dealing with the involvement of the ligands in these reactions [e.g. 28-30]. The mechanism has not been elucidated for all cases. Norton [28] proposes an intramolecular nucleophilic attack of a palladium bonded methyl group to a coordinated aryl ligand and explicitly excludes the intermediacy of phosphonium species, as deuterated phosphonium salts present in solution and having the same composition did not participate in the reaction. The mechanism involving phosphonium species will be discussed in the next section.

Aryl exchange via phosphonium intermediates. More recently a variation of the above mechanisms was reported by Novak [30]. Formally the mechanism also involves nucleophilic attack at coordinated phosphines, but after the nucleophilic attack the phosphorus moiety reductively eliminates from the metal as a phosphonium salt. To obtain a catalytic cycle the phosphonium salt re-adds to the zerovalent palladium complex (Figure 10).

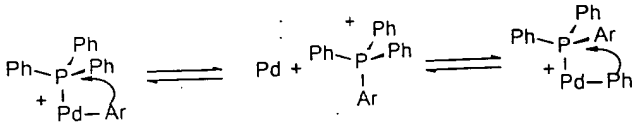

Figure 10. Aryl exchange via phosphonium formation

Scavenging of free phosphines by electrophiles such as protons, other metals, conjugated enones, etc. presents a potential route to phosphine loss in catalytic systems. As yet, the participation of phosphonium intermediates has not been reported for rhodium hydroformylation catalysts, but they could be easily conceived, especially when dienes or enones are also present.

9.3.4 Decomposition of phosphites

Phosphites are easier to synthesize and less prone to oxidation than phosphines. They are much cheaper than most phosphines and a wide variety can be obtained commercially as they are used as anti-oxidants. Disadvantages of the use of phosphites as ligands include several side reactions: hydrolysis, alcoholysis, trans-esterification, Arbusov rearrangement, O-C bond cleavage, P-O bond cleavage. Figure 11 gives an overview of these reactions. In hydroformylation systems at least two more reactions may occur, namely nucleophilic attack to aldehydes, and oxidative cyclizations with aldehydes.

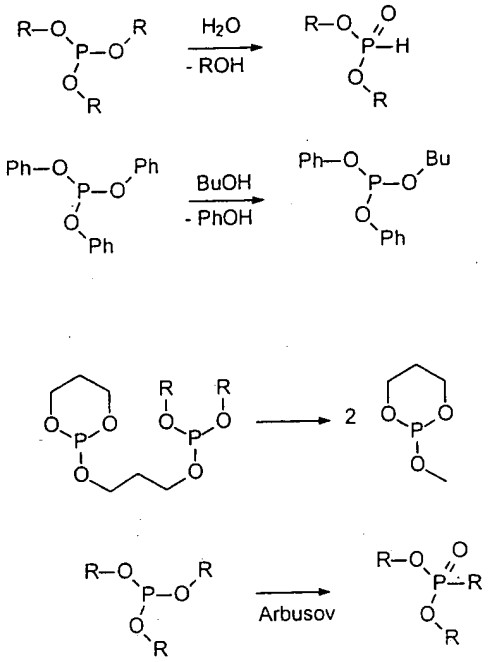

Figure 11. Decomposition pathways of phosphites

Phosphites have been extensively studied for their use as ligands in rhodium-catalyzed hydroformylation (see Chapter 3). The first publication on the use of phosphites is from Pruett and Smith, from Union Carbide [31]. The first exploitation of bulky monophosphites was reported by van Leeuwen and Roobeek [32]. They found that very high rates can be obtained for internal and terminal alkenes, but selectivities were low for linear alkenes. The bulky phosphites not only gave higher rates than less bulky phosphites, but they are also more resistant to hydrolysis. Bryant and coworkers [33] introduced even more stable, bulky phosphites by the

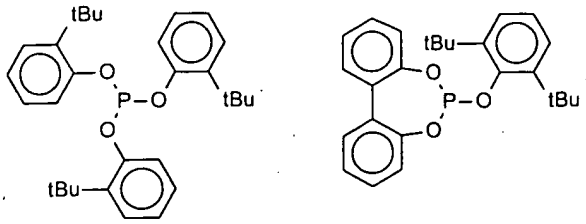

Figure 12. Bulky phosphite ligands

introduction of bisphenols instead monophenols for the phosphite synthesis (see Figure 12). High selectivities are only obtained when diphosphites are used.

Diphosphites came into focus after the discovery of Bryant and coworkers at Union Carbide Corporation that certain bulky diphosphites lead to high selectivities in the rhodium catalyzed hydroformylation of terminal and internal alkenes [34] (see Figure 13). A plethora of diphosphites has been tested and recorded in many patents authored by coworkers of several companies [35-37], indicating their importance for the near future in this field. The patents included in the references of this chapter serve only as examples.

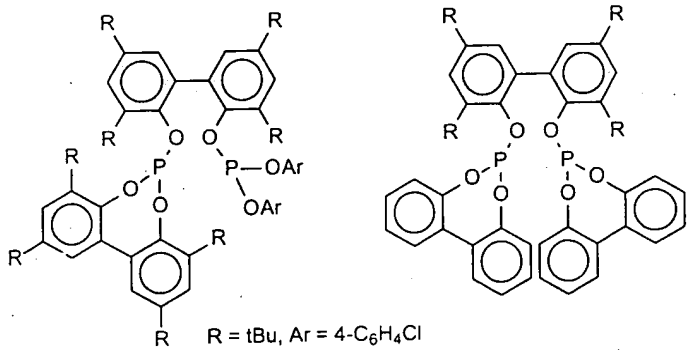

Figure 13. Examples of Union Carbide's diphosphites

The advantages of the diphosphite system for propene hydroformylation as compared to the commercial triphenylphosphine system are that less ligand and less rhodium are required and that higher rates can be obtained. Also high selectivities for conversion of internal alkenes to linear products have been reported.

It should be noted that all phosphites reported are aryl phosphites (sometimes the backbones may be aliphatic) and that the favored ones often contain bulky substituents. One of the reasons that aliphatic phosphites are used only sparingly is that they are susceptible to the Arbusov rearrangement

while the aryl phosphites are not. Acids, carbenium ions, and metals catalyze the Arbusov rearrangement. Many examples of metal catalyzed decomposition reactions have been reported [38, 39] (see Figure 14).

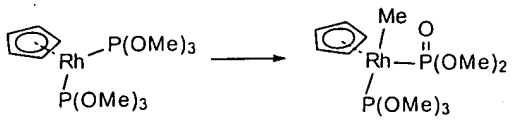

Figure 14. Metal catalyzed Arbuzov reaction

Thorough exclusion of moisture can easily prevent hydrolysis of phosphites in the laboratory reactor. In a continuous operation under severe conditions traces of water may form via aldol condensation of the aldehyde product. Weak and strong acids and strong bases catalyze the reaction. The reactivity for individual phosphites spans many orders of magnitude. When purifying phosphites over silica columns in the laboratory one usually adds some triethylamine to avoid hydrolysis on the column.

Bryant and coworkers have extensively studied decomposition of phosphites [40]. Stability involves thermal stability, hydrolysis, alcoholysis, and stability toward aldehydes. The precise structure has an enormous influence on the stability. Surprisingly it is the reactivity toward aldehydes that received most attention. Older literature [41] mentions several reactions between phosphites and aldehydes of which we show only two in Figure 15.

The addition of a phosphite to an aldehyde giving a phosphonate is the most important reaction [40]. The reaction is catalyzed by acid and since the product is acidic, the reaction is autocatalytic. Furthermore, acids catalyze hydrolysis and alcoholysis and therefore the remedy proposed is continuous removal of the phosphonate over a basic resin (Amberlyst A-21). The examples in the patents illustrate that very stable systems can be obtained when the acidic decomposition products are removed continuously.

The thermal decomposition of phosphites with aldehydes is illustrated in Figure 16 [40]. In this experiment the ligands are heated for 23 hours at 160 °C in the presence of pentanal. The figure shows the percentages of ligand that have decomposed as measured by NMR spectroscopy. This was done in the absence of a rhodium catalyst and so the numbers present a lower limit for the decomposition. One can see that minor effects in the ligand structure can have a tremendous influence on the rate of decomposition or rather the rate of reaction with aldehydes. While simple hydrolysis or alcoholysis might have been expected as the major source for ligand decomposition we see that a study to what is actually taking place is worthwhile as an attempt to stabilize the catalyst system.

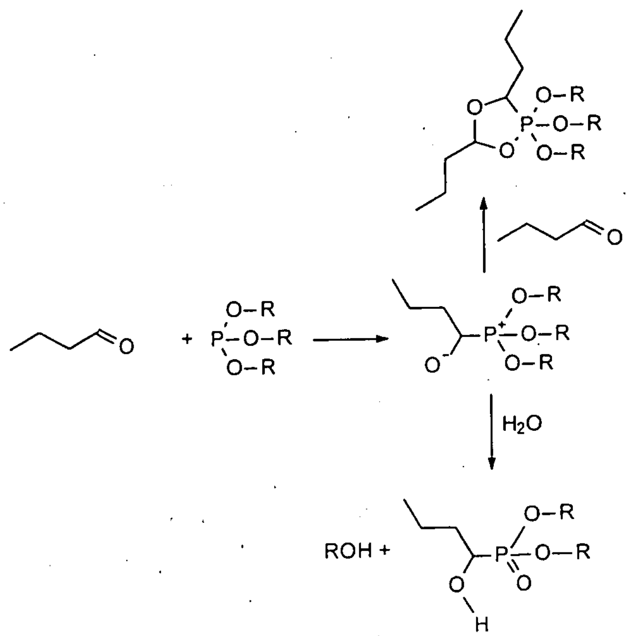

Figure 15. Reaction of phosphites with the aldehyde product

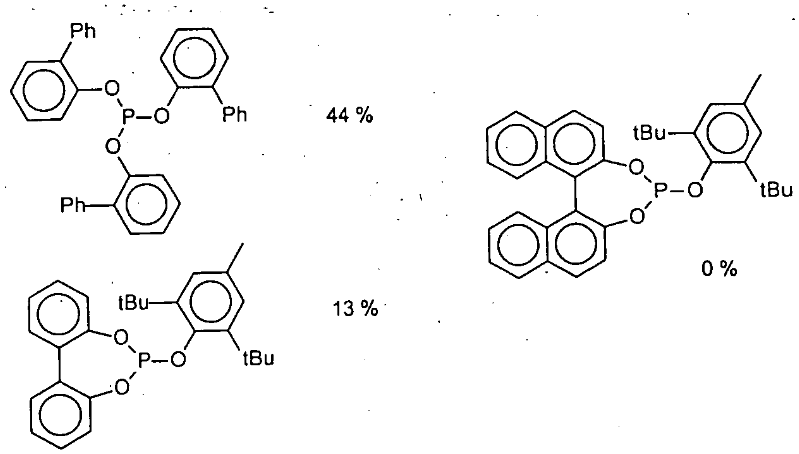

Figure 16. Stability of phosphites at 160 °C after 23 hours (see text for explanation; numbers give percentage of decomposition)

9.3.5 Formation of dormant sites

Dienes and alkynes are poisons for many alkene processes. In polyolefin manufacture they must be carefully removed as they deactivate the catalyst completely. Insertion of conjugated dienes is even much more rapid than insertion of ethene and propene. The resulting π-allyl species are inactive as catalysts.

In rhodium catalyzed hydroformylation the effect is less drastic and often remains unobserved, but surely diene impurities obscure the kinetics of alkene hydroformylation [42]. Because the effect is often only temporary we summarize it here under "dormant sites". Hydroformylation of conjugated alkadienes is much slower than that of alkenes, but also here alkadienes are more reactive than alkenes toward rhodium hydrides [43, 44]. Stable π-allyl complexes are formed that undergo very slowly insertion of carbon monoxide (Figure 17). The resting state of the catalyst will be a π-allyl species and less rhodium hydride is available for alkene hydroformylation. Thus, alkadienes must be thoroughly removed as described by Garland [45], especially in kinetic studies. It seems likely that 1,3- and 1,2-diene impurities in 1-alkenes will slow down, if not inhibit, the hydroformylation of alkenes.

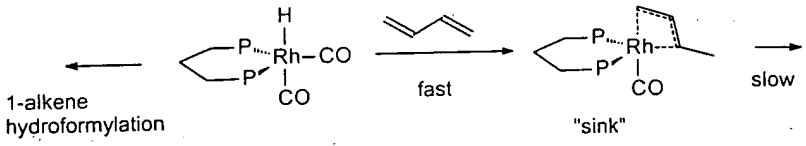

Figure 17. Reactions of diene to give π-allyl complexes

Dimer formation. Active, monomeric catalyst species may be involved the formation of inactive dimers. When this equilibrium is reversible it only leads to a reduction of the amount of catalyst available and it does not bring the catalysis to a full stop.

A well-known example is the formation of the so-called orange dimer from $HRh(PPh_3)_3CO$, already reported by Wilkinson [46]. Since then it has been reported by several authors [47 and references therein].

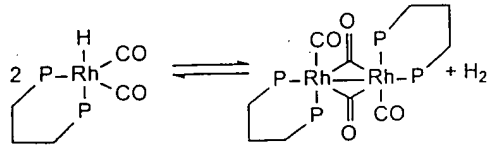

Figure 18. Dimer formation for hydroformylation catalysts

Since the hydroformylation reaction for most substrates shows a first order dependence in the concentration of rhodium hydride, the reaction becomes slower when considerable amounts of rhodium are tied up in dimers. This will occur at low pressures of hydrogen and high rhodium concentrations [47] (see Figure 18).

Work-up of hydroformylation solutions often leads to formation of dimers. It seems likely that in a liquid recycle of a continuous reactor rhodium will occur as such a dimeric species. Since the reaction with hydrogen is reversible it presents a means to recycle rhodium. Dimer formation is not restricted to phosphines as phosphites behave similarly [48].

When dimer formation becomes important one might attempt to destabilize the dimer relative to the monomer. For instance making the ligand very bulky might prevent dimer formation. Models show that the ligand size must be substantially increased to arrive at the desired effect. Another approach is so-called "site isolation" as was described by Grubbs [49]. His well-known example concerns a titanocene catalyst that is used as a hydrogenation catalyst. The intermediate titanium hydride is converted almost completely to a dimer rendering the catalyst with a low activity. Immobilization of the catalyst on a resin support prevents dimerization and an active catalyst is obtained.

Ligand metallation. In early transition metal polymerization catalysis often metalation of the ligand occurs leading to inactive catalysts. In late transition metal chemistry the same reactions occur, but now the complexes formed represent a dormant site and catalyst activity can often be restored. Work-up of rhodium-phosphite catalyst solutions after hydroformylation often shows partial formation of metallated species, especially when bulky phosphites are used [50]. Dihydrogen elimination or alkane elimination may lead to the metallated complex. The reaction is reversible for rhodium and thus the metallated species could function as a stabilized form of rhodium during a catalyst recycle. Many metallated phosphite complexes have been reported, but we mention only two, one for triphenyl phosphite and rhodium [51, 52] (see Figure 19) and one for a bulky phosphite and iridium [53].

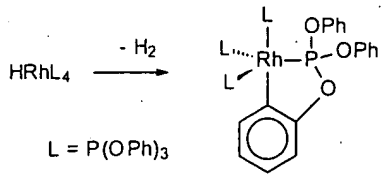

Figure 19. Metallation in rhodium phosphite complexes

9.4 Concluding remarks

Decomposition of organometallic catalysts under reaction conditions of catalytic processes lead to interesting organometallic chemistry. The study of this chemistry is often worthwhile either to find ways of circumventing the decomposition reactions or to find ways to work up the solutions such that the metal can be regenerated for further use and separated from the decomposed ligand fragments. From a stability viewpoint ligands having phosphorus as the donor atom are not very attractive, but for none of the metals active in hydroformylation (cobalt, platinum, palladium, rhodium) there seems to be an alternative other than carbon monoxide. Arsines lead to active catalysts, but it is not expected that they will form more stable complexes than phosphines. For several metal catalyzed reactions recently nitrogen ligands (Fe, Co, Pd) have been introduced which are often much more robust than phosphorus ligands. Rhodium hydride carbonyls do not seem to combine well with nitrogen ligands.

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